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FOLEY & LARDNER  
WASHINGTON HARBOUR P O BOX 25696  
3000 K STREET NW SUITE 500  
WASHINGTON DC 20007-8696

EXAMINER  
VANDERVEGT, F

ART UNIT	PAPER NUMBER
1816	#5

DATE MAILED: 07/22/97

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

Application No.  
**08/817,084**

Applicant(s)  
**Kishimoto et al**

Examiner  
**F. Pierre VanderVegt**

Group Art Unit  
**1816**



☒ Responsive to communication(s) filed on Jul 10, 1997

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), ~~or thirty days, whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claims

☒ Claim(s) 9-23 ~~is~~ are pending in the application.

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 9-23 ~~is~~ are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been  
☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). \_\_\_\_\_

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

### DETAILED ACTION

This application is a 371 of PCT/JP95/01144.

The specification on page 1 should be amended to reflect the priority information and status of the priority documents.

5           Claims 1-8 have been canceled. Claims 9-23 are currently pending in this application.

### *Specification*

1.       This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

10           2.       The disclosure is objected to because of the following informalities: The claims should read in the form of a complete sentence beginning with "I/We claim" or "What is claimed is" and ending with a period. It is suggested that the word "CLAIMS" at the top of page 53 in the specification be replaced with --We claim-- or --What is claimed is--.

15           Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

20           3.       Claims 10 and 19-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

25           The claims are drawn to a method for the in vivo inhibition of synovial cell growth by the administration of an antagonist of IL-6 activity, with specific claims to antibodies directed to either IL-6 or IL-6 receptor. The specification does not provide disclosure enabling for these claims. The specification provides two working examples, the first of which is an in vitro

experiment with cultured synovial cells (Example 1, pages 22-23 of the instant specification). The cells are incubated with IL-6 and soluble IL-6 receptor, which stimulates growth of the cells, and then treated with antibodies to IL-6 or to IL-6 receptor, which ablates the growth stimulation of the IL-6 and soluble IL-6 receptor. Example 2 (pages 23-25 of the instant specification) details an experiment in which mice that are subjected to collagen-induced arthritis are treated with an anti-IL-6 receptor antibody, resulting in a reduction of joint swelling. While the specification shows that the antibodies can inhibit in vitro growth of synovial cells which are exogenously treated with supplemental IL-6 and soluble IL-6 receptor, the cultured cells were not subjected to additional cytokines which are growth inducing, as they would be subjected to in vivo. Further, while the murine in vivo model shows a reduction of swelling as a result of treatment with anti-IL-6 receptor antibody, it cannot be directly assumed that this reduction is due to inhibition of the growth of synovial cells, as it is well known in the art that swelling of rheumatic joints is associated with a multiplicity of factors affected by various cytokines, including among others the infiltration of immune cells and build-up of synovial fluid. Given the nature of the invention, which is the inhibition of synovial cell growth, the limited nature of the working examples and the lack of guidance in the specification, a skilled artisan would not be able to reasonably predict the in vivo inhibition of synovial cells by antibodies to IL-6 or to IL-6 receptor within an environment rich in stimulatory cytokines.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. Claims 9 and 17 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by U.S. Patent 5,591,827 (A on form PTO-892).

5 The '827 patent teaches pharmaceutical compositions comprising therapeutically effective amounts of IL-6 antagonists and a pharmaceutically acceptable carrier (Claims 12-20 in particular) for the treatment of human patients with IL-6 related diseases (Abstract in particular), including rheumatoid arthritis (Column 4, lines 3-8 in particular). The prior art teaching clearly anticipates the claimed invention.

***Claim Rejections - 35 USC § 103***

10 The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

15 (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

20 This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

25 5. Claims 9 and 17-18 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over U.S. Patent 5,591,827 (A).

The '827 patent has been discussed supra. The '827 patent is silent about divided doses of 1 to 1000 mg each but does teach the presence of a therapeutically effective amount of the IL-6

agonist being comprised in the pharmaceutical compositions. Therefore, the method of the instant application and that of the '827 patent appear to be the same or similar absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious.

In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See *In re Best* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

6. Claims 9 and 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,591,827 (A) in view of Sipe et al (U) and U.S. Patent 5,559,012 (B).

The '827 patent has been discussed supra. The '827 patent does not teach antibodies to IL-6. The Sipe et al reference teaches that the destruction of joints caused by rheumatoid arthritis is due in part to the action of destructive cytokines such as IL-1 and IL-6 and can be modulated at multiple points associated with either cytokine action or production (Abstract in particular). Sipe et al further teach that potential agents for this modulation include anti-cytokine and anti-cytokine receptor antibodies (Abstract in particular). The '012 patent teaches a therapeutic kit which comprise monoclonal antibodies which antagonize the mediator to which they are raised (Column 4, lines 1-7 in particular) and bind to IL-6 and block its biological activity (Claims 1-10 in particular). Exemplary pharmaceutical compositions taught by the '012 patent consist of 1 mg of each monoclonal antibody with a pharmaceutically acceptable carrier (column 13, lines 46-67 in particular). It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use the monoclonal antibodies taught by the '012 patent in a manner consistent with the '827 patent. One would have been motivated to combine the references with a reasonable expectation of success by the teachings of Sipe et al that monoclonal

7. Claims 9 and 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,591,827 (A) in view of Sipe et al (U), U.S. Patent 5,559,012 (B) and Hirata et al (A4 on form PTO-1449).

The '827 and '012 patents and Sipe et al have been discussed supra. The combined references do not teach monoclonal antibody to IL-6 receptor. Hirata et al teach a monoclonal antibody (PM1) which binds to an epitope on the IL-6 receptor and blocks the binding of IL-6 to the receptor (Abstract in particular). It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to substitute the PM1 monoclonal antibody taught by Hirata et al for the monoclonal antibodies of the '012 patent for administration in a manner consistent with the '827 patent. One would have been motivated to combine the references with a reasonable expectation of success by the teachings of Sipe et al that monoclonal antibodies to cytokine receptors are effective agents for blocking the destructive action of cytokines in rheumatoid arthritis and the teachings of the Hirata et al that the PM1 monoclonal antibody is effective for blocking IL-6 binding to the receptor.

## Conclusion


8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

9. Papers related to this application may be submitted to group 1800 by facsimile transmission. Papers should be faxed to group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone numbers for official documents to be entered into the record for Art Unit 1816 are (703)305-3014 or (703)308-4242. *Communications which*

*are not to be entered into the record, such as proposed amendments, should be clearly marked "DRAFT" and faxed to (703)305-7939.*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt, whose telephone number is (703)305-6997. The examiner can normally be reached Monday through Friday from 8:00 am to 4:30 pm ET. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Christina Chan can be reached at (703)308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the group 1800 receptionist, whose telephone number is (703)308-0196.

July 20, 1997  
F. Pierre VanderVegt, Ph.D.  
Patent Examiner  
Art Unit 1816

  
FRANK C. EISENSCHENK  
PRIMARY EXAMINER  
GROUP 1800  
7/21/97